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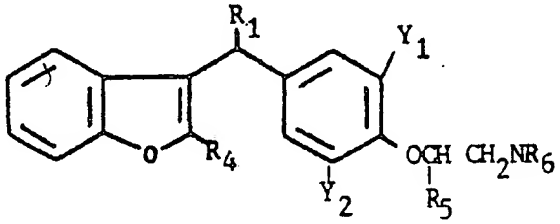
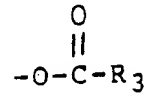
(54) Title: CERTAIN 3-SUBSTITUTED 2-ALKYL BENZOFURAN DERIVATIVES



(I)



(II)

(57) Abstract

The disclosure relates to compounds of formula (I) and pharmaceutically acceptable addition salts thereof wherein R_1 represents hydrogen, R_1 represents a group having the formula $-OR_2$ in which R_2 is a lower alkyl group or an aryl group, or R_1 represents a group having formula (II), in which R_3 is hydrogen, a lower alkyl group, or an aryl group, wherein R_4 is a saturated lower alkyl group containing 1 to 6 carbon atoms, wherein R_5 is either hydrogen or methyl, wherein NR_6 is a group selected from the class consisting of amino, lower mono and dialkylamino, piperidino, pyrrolidono, and morpholino groups and wherein Y_1 and Y_2 are identical and are hydrogen or a halogen. Compounds in accordance with the invention are useful as vasodilators and as antiarrhythmic agents.

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CERTAIN 3-SUBSTITUTED 2-ALKYL BENZOFURAN DERIVATIVES

Technical Field

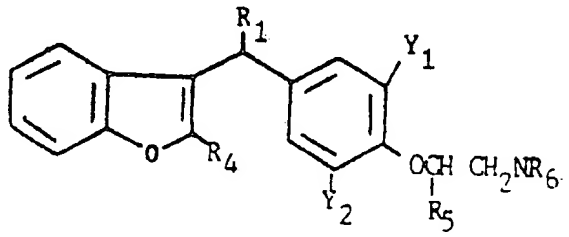
The invention relates to compounds having pharmacological activity and more particularly relates to novel pharmacologically active 3-substituted 2-alkyl benzofuran derivatives, and methods for their preparation.

Background Art

Compounds as disclosed herein are not known to exist in the prior art. Ketones used in the synthesis of certain of the claimed compounds are disclosed in U.S. Patent 3,248,401.

Disclosure of the Invention

Compounds in accordance with the invention are represented by the general formula:



I

and pharmaceutically acceptable addition salts thereof wherein R_1 represents hydrogen, R_1 represents a group having the formula $-OR_2$ in which R_2 is a lower alkyl group or an

aryl group, or R_1 represents a group having the formula $-O-\overset{O}{\overset{\|}{C}}-R_3$ in which R_3 is hydrogen, a lower alkyl group, or an aryl group, wherein R_4 is a lower alkyl group containing 1 to 6 carbon atoms, wherein R_5 is either hydrogen or methyl, wherein NR_6 is a group selected from the class consisting of amino, lower mono and dialkylamino, piperidino, pyrrolidino, and morpholino groups and wherein Y_1 and Y_2 are identical and are hydrogen or a halogen.

The term "lower alkyl" as used in this written description of the invention is intended, unless further defined, to designate a straight-chain, branched aliphatic hydrocarbon group containing between 1 to 18 carbon atoms, e.g. methyl, ethyl, isopropyl, tertiary butyl, cyclohexyl, and the like. "Aryl" refers to substituted or unsubstituted aromatic hydrocarbon groups, e.g. phenyl, naphthyl, benzyl, and the like. "Lower mono and dialkylamino" refers to amino groups with one or two straight-chain, branched aliphatic hydrocarbon groups containing I - 6 carbon atoms. When two groups are present, they may be the same or different. Examples are methylamino, dimethylamino, ethylamino, diethylamino, n-propylamino, isopropylamino, and the like. Halogen, unless further defined, is intended to refer to fluorine, chlorine, bromine, and iodine.

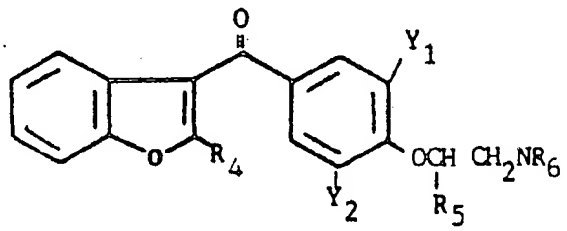
Compounds in accordance with the invention are useful as vasodialators and as antiarrythmic agents. Preferred for this purpose are compounds of the Formula I above wherein R_1 is hydrogen or $-OR_2$ with R_2 being a lower alkyl group containing between 1 and 6 carbon atoms, or R_1 is $-O-\overset{O}{\overset{\|}{C}}-R_3$ with R_3 being hydrogen, or a lower alkyl group

containing between 1 and 6 carbon atoms, R_4 is butyl, R_5 is hydrogen, NR_6 is amino or lower mono and dialkylamino and Y_1 and Y_2 are identical and are hydrogen, bormine or iodine. Most preferably, R_1 is hydrogen or $-OR_2$ with R_2 being a lower alkyl group containing between 1 and 4 carbon atoms, or R_1 is

$-O-\overset{O}{\overset{\|}{C}}-R_3$ with R_3 being hydrogen or a lower alkyl group containing 1 to 4 carbon atoms, R_4 is n-butyl, R_5 is hydrogen, NR_6 is amino, ethylamino or diethylamino and Y_1 and Y_2 are either both hydrogen or both iodine.

Best Mode of Carrying Out the Invention

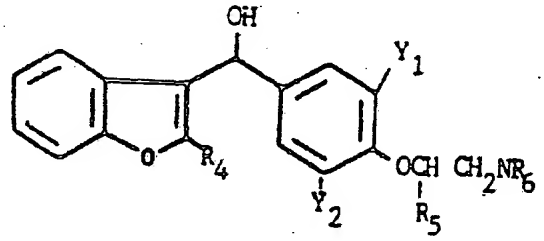
The novel compounds of Formula I above are advantageously prepared by way of an alcohol intermediate which is produced by reducing a ketone of the formula:



II

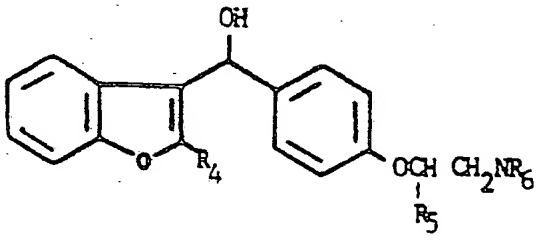
with R_4, R_5, NR_6, and Y_1 and Y_2 as defined for Formula I. Formula II ketones are known and procedures for their synthesis are described in U.S. Patent No. 3,248,401, the disclosure of which is incorporated by reference. To produce compounds according to Formula I wherein Y_1 and Y_2 are identical halogens, reduction of the compounds of

Formula II with Y_1 and Y_2 being halogens is performed under conditions which reduce the ketone group to the alcohol without otherwise affecting the molecule. A reducing system employing sodium borohydride in a tetrahydrofuran-methanol mixture (10:1 v/v) at approximately 0°C produces high yields of the alcohol represented by Formula III:



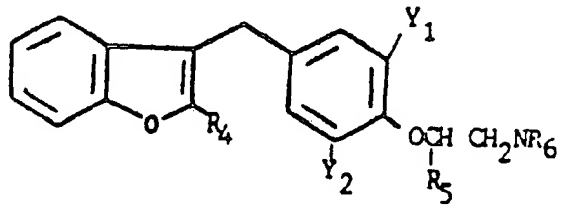
III

To prepare compounds of the invention wherein Y_1 and Y_2 are both hydrogen, the ketones of the Formula II wherein Y_1 and Y_2 are both hydrogen are similarly reduced to produce the alcohol intermediate shown in Formula IV. Alternately, reduction of Formula II compounds wherein Y_1 and Y_2 are both halogens employing a reduction system which reduces the ketone group to the alcohol while also dehalogenating the benzene ring produces Formula IV alcohols. Sodium borohydride in methanol in the presence of a $PdCl_2$ catalyst at 20°C is a preferred reduction system to achieve both reduction and dehalogenation.

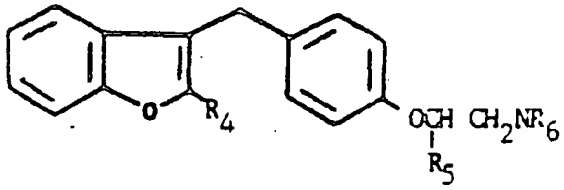


IV

Compounds of Formula I wherein R_1 is hydrogen are produced from the intermediates of Formulas III and IV by further reduction of the alcohol group. Compounds of Formula III (halogenated) or IV (dehalogenated), when reacted in a suitable solvent as 0°C with sodium borohydride in trifluoroacetic acid produce compounds of Formulas V and VI, respectively.



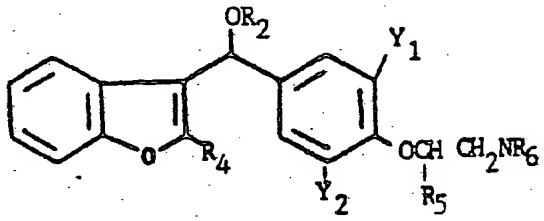
V



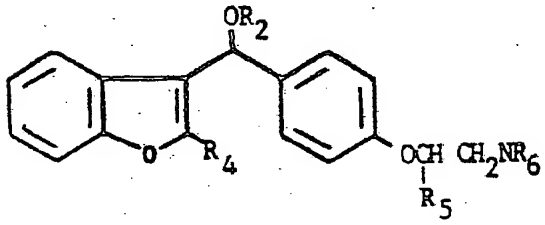
VI

The alcohols of Formulas III and IV are also employed as intermediates to produce compounds wherein R_1

is $-OR_2$ and R_2 is alkyl or aryl. A Williamson synthesis whereby the alcohols of Formula III or VI are converted to the corresponding alkoxide and reacted with an alkyl or aryl halide of the formula R_2X is used to produce the ethers represented by Formulas VII (halogenated) and VIII (dehalogenated).



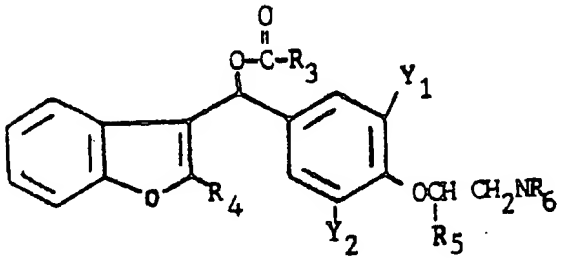
VII



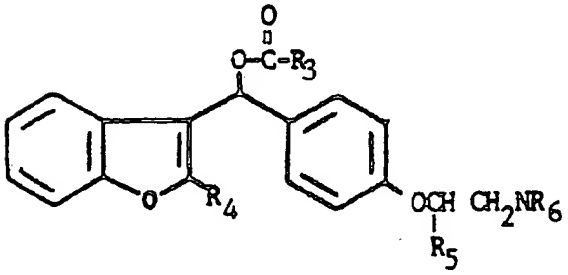
VIII

To produce the compounds of Formula I wherein R_1 is $-O-\overset{O}{\overset{\|}{C}}-R_3$, the alcohols of Formulas III and IV are

esterified. Acyl halides of the formula R_3-C-X can be reacted with the alcohols of Formulas III or IV, respectively, preferably in the presence of a solvent capable of acting as an acid scavenger, e.g. pryridine, to produce compounds of Formulas IX (halogenated) or X (dehalogenated), respectively:



IX



X

The compounds of Formula I form acid addition salts with pharmaceutically acceptable acids, for example, with

inorganic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and with organic acids such as acetic acid, tartaric acid, maleic acid, citric acid and toluenesulfonic acid.

The compounds of the Formula I above and the salts thereof are useful in treating arrhythmic conditions and conditions for which treatment with a vasodialator is indicated. The novel pharmaceutically active agents provided by the present invention can be administered in pharmaceutical dosage forms, internally, for example, parenterally or enterally with dosage adjusted to fit the exigencies of the therapeutic situation. The pharmaceuticcal dosage forms are prepared by incorporating the active ingredient in conventional liquid or solid vehicles to thereby provide emulsions, suspensions, tablets, capsules, powders and the like according to acceptable pharmaceutical practices. A wide variety of carriers of diluents as well as emulsifying agents, dispersing agents and other pharmaceutically acceptable adjuvants can be incorporated in the pharmaceutical dosage forms.

The following examples are offered to illustrate the invention and are not intended to be limiting.

EXAMPLE I

Preparation of (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl] methanol.

One 1 mmole (645 mg) of the ketone (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl] - methanone is dissolved in 30 ml of THF:MeOH (10:1 v/v). Sodium borohydride (1.2 mmole, 45.42 mg) is added to the solution and the mixture is stirred and maintained at a temperature of 0°C until the starting

material is consumed (~15 minutes). Excess borohydride is destroyed by the dropwise addition of water (0.5 ml). Volatile components are removed under reduced pressure (roto-evaporator). Water is added to the residue (10 ml) followed by the addition of methylene chloride (~10 ml). The methylene chloride layer is separated form the aqueous phase and is dried over anydrous sodium sulfate. The methlyene chloride solvent is removed under reduced pressure and the product is purified by column chromatography (silica gel support using methylene chloride) and is recovered by reduced pressure evaporation of the methylene chloride. The yield of the product, m.p. 106-107°C, is >50% of theoretical. (The m.p. of the hydrochloride salt is 143-145°C.)

EXAMPLE II

Preparation of (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-phenyl] methanol.

One mmole (645 mg) of the ketone, (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl] methanone is dissolved in 10 ml of methanol. Palladium dichloride (2mmole, 354 mg) is added and the mixture is agitated to suspend the palladium dichloride. The temperature of the mixture is adjusted to 20°C. Sodium borohydride (10 mmole, 379 mg) is added and stirring is continued until reaction is complete (~1 hour). The palladium dichloride is removed by filtration and water is added to the filtrate. An ether extraction is performed and the product is removed fro the ether phase by evaporation under reduced pressure. The produce is purified by chromatography (silica gel using methylene chloride) and results in >50% yield of the product, m.p. 203°C (decomposes).

EXAMPLE III

Preparation of (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl] methane.

One mmole (647 mg) of the alcohol as prepared in EXAMPLE I is dissolved in methylene chloride (5 ml). Sodium borohydride (38 mg, 10 mmole) added to 10 ml of trifluoroacetic acid and the mixture is cooled to 0°C. The methylene chloride solution is added slowly to the trifluoacetic acid solution and the mixture stirred for 30 minutes at 0°C. Excess borohydride is destroyed by the dropwise addition of water (0.5 ml). Volatile components are removed under reduced pressure (roto-evaporator). Water is added to the residue (25 ml) followed by the addition of methylene chloride (25 ml). The methylene chloride layer is separated, washed twice with 25 ml of 5% aqueous sodium hydroxide and 25 ml of water. The methylene chloride solution is dried over sodium sulphate and then passed through a short (~5 cm) basic alumina column. Evaporation of the solvent yields the product, m.p. 80-81°C, in >70% yield. (The m.p. of the hydrochloride salt is 119-121°C.)

EXAMPLE IV

Preparation of methoxy (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl] methane.

One mmole (647 mg) of the alcohol as prepared in EXAMPLE I is dissolved in 10 ml of THF. The solution is cooled to -78°C and lithium diisopropylamide in cyclohexane (1.1 mmole, 0.73 ml of a 1.5 M solution) is slowly added. Methyl iodide (1.2 mmole, 0.17 g) is added and the mixture permitted to warm to room temperature (~30 minutes). The volatile components are removed under reduced pressure (roto-evaporator) and the residue is dissolved in methylene

chloride. The methylene chloride solution is dried over anhydrous sodium sulfate and is purified by passing the solution through silica gel column as in EXAMPLE I. The product, m.p. 96-98°C, is obtained upon evaporation of the solvent in a theoretical yield of >90%.

EXAMPLE V

Preparation of (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl] methyl pivalate.

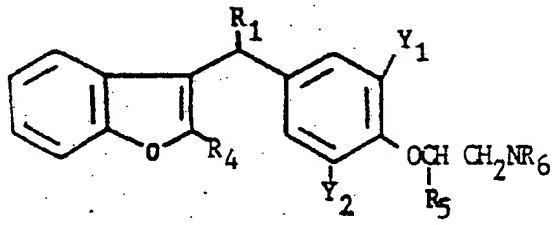
One mmole (647 mg) of the alcohol as prepared in EXAMPLE I is dissolved in pyridine (4 ml). Excess pivaloyl chloride (5 mmole, 605 mg) is added to the pyridine solution and the mixture heated to 65°C until the starting alcohol is completely consumed (approximately 12 hours). Volatile materials are removed under reduced pressure (roto-evaporator). The residue is dissolved in methylene chloride and the methylene chloride solution washed twice with 25 ml of 5% aqueous sodium hydroxide and once with 25 ml of water. The methylene chloride solution is dried over sodium sulfate and then passed through a short (~5 cm) basic alumina column. Evaporation of the solvent yields the product in >90% yield. (The m.p. of the hydrochloride salt is 108-110°C.)

Industrial Applicability

Compounds in accordance with the invention are useful as vasodialators and as antiarrhythmic agents.

THE CLAIMS:

1. A compound of the formula:



and pharmaceutically acceptable addition salts thereof wherein R_1 is selected from the class consisting of hydrogen, a group having the formula $-OR_2$ in which R_2 is a lower alkyl group or an aryl group consisting of phenyl, napthyl, benzyl and substituted derivatives thereof, and a group having the formula $-O-\overset{O}{\overset{\|}{C}}-R_3$ in which R_3 is hydrogen, a lower alkyl group, or an aryl group, consisting of phenyl, napthyl, benzyl and substituted derivatives thereof wherein R_4 is a lower alkyl group containing 1 to 6 carbon atoms, wherein R_5 is either hydrogen or methyl, wherein NR_6 is a group selected from the class consisting of amino, lower mono and dialkylamino, piperidino, pyrrolidino, and morpholino groups and wherein Y_1 and Y_2 are identical and are selected from the class consisting of hydrogen and halogen.

2. A compound as set forth in Claim 1 wherein R_1 is selected from the class consisting of hydrogen, a group having the formula $-OR_2$ with R_2 being a lower alkyl group containing between 1 and 6 carbon atoms, and a group having

the formula $-O-\overset{O}{\overset{\|}{C}}-R_3$ with R_3 being hydrogen or a lower alkyl group containing between 1 and 6 carbon atoms, R_4 is butyl, R_5 is hydrogen, NR_6 is selected from the class consisting of amino and lower mono and dialkylamino and Y_1 and Y_2 are identical and are selected from the class consisting of hydrogen, bromine, and iodine.

3. A compound as set forth in Claim 1 wherein R_1 is selected from the class consisting of hydrogen, a group having the formula $-OR_2$ with R_2 being a lower alkyl group having between 1 and 4 carbon atoms, and a group having the formula $-O-\overset{O}{\overset{\|}{C}}-R_3$ with R_3 being hydrogen or a lower alkyl group containing 1 to 4 carbon atoms, R_4 is n-butyl, R_5 is hydrogen, NR_6 is selected from the class consisting of amino, ethylamino, and diethylamino, and Y_1 and Y_2 are identical and are selected from the class consisting of hydrogen and iodine.

4. A compound according to Claim 1 wherein said compound is (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-3,5 diiodophenyl] methane.

5. A compound according to Claim 1 wherein said compound is (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-phenyl] methane.

6. A compound according to Claim 1 wherein said compound is methoxy (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl] methane.

7. A compound according to Claim 1 wherein said compound is methoxy (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-phenyl] methane.

8. A compound according to Claim 1 wherein said compound is (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl] methyl pivalate.

9. A compound according to Claim 1 wherein said compound is (2-n-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxyl]-phenyl] methyl pivalate.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/01060

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): C07D 307/80

U.S.Cl.: 549/471; 544/153; 546/196; 548/525

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	549/471; 544/153; 546/196; 548/525

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	U.S., A, 3,248,401 (TONDEUR ET AL) 26 April 1966. See the entire document.	1-11

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

24 MAY 1988

Date of Mailing of this International Search Report

22 JUN 1988

International Searching Authority

ISA/US

Signature of Authorized Officer

Bernard Dentz

BERNARD DENTZ